Hayes et al. recite a method for making an apparatus to conduct biochemical analyses using flex circuit manufacturing techniques (see col. 7, lines 28-45) involving assembling a device composed of a series of planar layers, some metallic and some non-metallic. Therefore, all conductive structures in the apparatus disclosed by Hayes are confined to the two-dimensional 'metallic' layers.

Wilding discloses a variety of devices fabricated utilizing micromachining methods such as photolithography, etching and deposition techniques, laser machining and LIGA processing (see col. 7, lines 22-38). Utilizing the disclosed methods results in a planar configuration, wherein channels, chambers, and electrical connections would be confined to a 2-dimensional plane, as can be readily seen in Wilding's Figs. 2A, 2B, and 5, for example.

In contrast, Applicants disclose devices fabricated by sintering together a plurality of green-sheets. The green-sheets may be patterned prior to sintering, and thick-film pastes may be applied to the green-sheets prior to sintering. This process results in devices having features distributed three-dimensionally throughout.

Applicants note that a prima facie case of obviousness requires some suggestion or motivation, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, to modify the reference teachings. In addition, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (See M.P.E.P. §2142).

Applicants submit that neither reference, either alone or in combination, provides the motivation or suggestion to combine the references.

The Examiner has a number of statements regarding motivation: the Examiner states that the "motivation to use a ceramic material in the fabrication of the apparatus taught by Hayes et al. Would have been to facilitate effective thermal isolation of each of the wells", that "it is deemed reasonable that one of ordinary skill in the art would have contemplated the incorporation of a thermally insulating material within these regions and therefore institute the fabrication of the entire supporting substrate **20** using this thermally insulating material" and that "[t]he motivation to use a thermally insulating material for the fabrication of the supporting substrate would have been to effectively thermally isolate each of the reaction chambers from one another in order to provide effective temperature cycling control". All of these statements do not find support in either reference; rather, the Examiner is relying on a "common sense" or "common knowledge" type of motivation to support a finding of non-obviousness. However, as the Board of Patent Appeals and Interferences held in In re Lee, 61 USPQ2d 1430 (CA FC 2002), "common knowledge" or "common sense" is not suitable motivation under 35 U.S.C. §103.

Further, the Examiner suggests that the motivation to combine ceramic materials disclosed by Wilding with the device recited in Hayes would be to thermally isolate the wells. However, Applicants

submit that the Wilding reference does not disclose or suggest thermally isolating a plurality of wells using ceramic materials. Instead, the only recitation of ceramic materials in the Wilding reference is a brief disclosure that devices described by Wilding may be fabricated on a ceramic substrate (col. 14, line 31). However, other materials are recited in the same spirit which are clearly not suitable for thermally isolating wells - such as steel, gold, silver, copper, tungsten, and the like (col. 14, line 30-31). The Examiner is respectfully directed to Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 230 USPQ 416 (Fed. Cir. 1986) where the Federal Circuit held that a single line in a prior art reference should not be taken out of context and relied upon to show obviousness under 35 U.S.C. § 103. Rather, the Federal Circuit held that a prior art reference should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered. Applicants submit that Wilding does not disclose thermal insulation of wells as an intended use of ceramic materials. Accordingly, Applicants submit that a motivation to combine Hayes and Wilding is not present, and the rejection is improper.

Further, Applicants submit that Hayes and Wilding, alone or in combination, fail to disclose or suggest all limitations of Applicants' claim 1, including "a substantially monolithic structure formed from a plurality of green-sheet layers sintered together, said green-sheet layers including particles selected from the group consisting of ceramic particles, glass particles, and glass-ceramic particles". Hayes discloses a device formed from alternating metallic and non-metallic layers. Wilding discloses devices formed through conventional micromachining techniques. Neither disclose or suggest the use of green-sheet layers.

Claims 2, 6-8, 10, 14, 17-23, and 28-33 depend from and include all limitations of base claim 1. Accordingly, Applicants submit that the 35 U.S.C. §103(a) rejection of claims 1, 2, 6-8, 10, 14, 17-23, and 28-33 over Hayes in view of Wilding is improper, and should be withdrawn.

Claims 33-35 further introduce new features not disclosed or suggested by Hayes, Wilding, or the combination of the references. Claim 33 recites heaters, "wherein each of said heaters comprise coils forming loops around each of said well structures along a length of said well structures." New claim 34 recites "electrical connections to said well structures distributed three-dimensionally within said substantially monolithic structure". New claim 35 recites "conductive pathways extending along and into the device, wherein the pathways make electrical connection to said heaters, coolers, or temperature monitors". As discussed above, Hayes and Wilding, taken alone or in combination, fail to disclose or suggest the three-dimensional nature of the features recited in claims 33-35. Applicants respectfully submit that the features recited in claims 33-35 are unattainable utilizing the planar flex circuit techniques of Hayes or the micromachining techniques of Wilding. Accordingly, Applicants submit that claims 33-35 are patentable over Hayes and Wilding for the reasons applied to claim 1 above, and further for limitations introduced in those claims.

Claims 11, 12, and 27 were rejected under 35 U.S.C. §103(a) as being unpatentable over Hayes et al. in view of Wilding et al. as applied to claims 1, 2, 6-8, 10, 14, 17-23 and 28-33 above, and further in view of Anderson et al. (U.S. Patent Number 6,168,948).

Hayes and Wilding are discussed above.

Anderson et al. is directed toward a miniaturized genetic analysis system. The devices of Anderson, similar to those of Wilding, are fabricated with conventional microfabrication techniques (col. 18, line 58 - col. 20, line 17).

In contrast, and as discussed above, Applicants disclose devices fabricated by sintering a plurality of green-sheets together.

As discussed above, a prima facie case of obviousness requires that the prior art reference (or references when combined) must teach or suggest all the claim limitations. (See M.P.E.P. §2142).

Applicants submit that Hayes, Wilding, and Anderson, taken alone or in combination fail to disclose all limitations of Applicants' amended claim 1, including a "substantially monolithic structure formed from a plurality of green-sheet layers sintered together, said green-sheet layers including particles selected from the group consisting of ceramic particles, glass particles, and glass-ceramic particles". Claims 11, 12, and 27 depend from and include all limitations of claim 1. Accordingly, Applicants respectfully submit that the 35 U.S.C. §103(a) rejection of claims 11, 12, and 27 over Hayes in view of Wilding and further in view of Anderson is improper and should be withdrawn.

Claims 15 and 16 were rejected under 35 U.S.C. §103(a) as being unpatentable over Hayes et al. in view of Wilding et al. as applied to claims 1, 2, 6-8, 10, 14, 17-23 and 28-33 above, and further in view of Burns et al. (U.S. Patent Number 6,057,149).

Hayes and Wilding are discussed above.

Burns is directed toward microscale devices. Burns, as Anderson above, discloses the use of conventional planar microfabrication technologies (col. 10, line 51 - col. 12, line 48).

In contrast, and as discussed above, Applicants disclose devices fabricated by sintering a plurality of green-sheets together.

As discussed above, a prima facie case of obviousness requires some suggestion or motivation, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, to modify the reference teachings. In addition, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (See M.P.E.P. §2142).

Applicants submit that none of the references, either alone or in combination, provides the motivation or suggestion to combine the references.

A lack of motivation to combine Hayes and Wilding is discussed above. The Examiner suggests that the motivation to integrate a metal wire heater into the structure would be for effective temperature control of the wells. However, Burns is directed toward the use of heaters for differentially reducing the surface tension of a droplet such that the operation of sequential heaters results in motion of the droplet. Temperature control of wells is not suggested in the reference. Accordingly, Applicants submit that the rejection is improper and should be withdrawn.

Further, Applicants submit that Hayes, Wilding, and Burns, taken alone or in combination fail to disclose all limitations of Applicants' amended claim 1, including a "substantially monolithic structure formed from a plurality of green-sheet layers sintered together, said green-sheet layers including particles selected from the group consisting of ceramic particles, glass particles, and glass-ceramic particles". Claims 15 and 16 depend from and include all limitations of claim 1. Accordingly, Applicants respectfully submit that the 35 U.S.C. §103(a) rejection of claims 15 and 16 over Hayes in view of Wilding and further in view of Burns is improper and should be withdrawn.

Claim 23 was rejected under 35 U.S.C. §103(a) as being unpatentable over Hayes et al. in view of Wilding et al. as applied to claims 1, 2, 6-8, 10, 14, 17-23 and 28-33 above, and further in view of Kellogg et al. (U.S. Patent Number 6,063,589).

Hayes and Wilding are discussed above.

Kellogg discloses manufacturing devices from machined acrylic (see col. 37, lines 29-37 and col. 39, lines 26-36). Kellogg further discloses screen-printing resistive and conductive inks for use as heaters (see col. 31, line 56 - col. 32, line 2).

In contrast, and as discussed above, Applicants disclose devices fabricated by sintering a plurality of green-sheets together.

As discussed above, a prima facie case of obviousness requires that the prior art reference (or references when combined) must teach or suggest all the claim limitations. (See M.P.E.P. §2142).

Applicants submit that Hayes, Wilding, and Kellogg, taken alone or in combination fail to disclose all limitations of Applicants' amended claim 1, including a "substantially monolithic structure formed from a plurality of green-sheet layers sintered together, said green-sheet layers including particles selected from the group consisting of ceramic particles, glass particles, and glass-ceramic particles". Claim 23 depends from and includes all limitations of claim 1. Accordingly, Applicants respectfully submit that the

35 U.S.C. §103(a) rejection of claim 23 over Hayes in view of Wilding and further in view of Kellogg is improper and should be withdrawn.

New Claims

Applicant has added new claims 34 and 35 which further distinguish over the cited art. For example, Claim 34 recites "electrical connections to said well structures distributed three-dimensionally within said substantially monolithic structure", and claim 35 recites "conductive pathways extending along and into the device, wherein the pathways make electrical connection to said heaters, coolers, or temperature monitors". The cited art fails to disclose or suggest these features. Other of the added claims present other features that are neither disclosed nor suggested by the cited art.

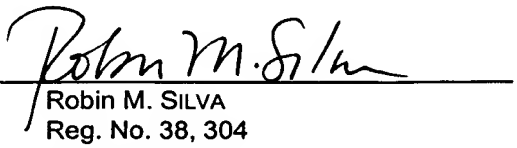
CONCLUSION

Applicants respectfully submit that the cited references, taken alone or in combination, fail to disclose or suggest all limitations of Applicants' claims 1, 1, 2, 6-8, 10-12, 14-23, and 26-35. Accordingly, Applicants submit that the 35 U.S.C. §103(a) rejections of the claims be withdrawn, and that the claims are in condition for allowance. The Examiner is invited to telephone the undersigned attorney in the event that further issues are identified that would preclude allowance of the claims.

While Applicant believes that no further fees are due at this time, the Commissioner is authorized to charge any fees that may be due as a result of filing this amendment, including additional claims fees not already paid for, or other fees that have not been separately paid, to Deposit Account 50-2319 (Order No. 469008-00156 [A-70143]).

Respectfully submitted,

DORSEY & WHITNEY LLP

By 
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APPENDIX WITH MARKINGS SHOWING CHANGES MADE

Claims 1, 16, and 33 were amended as follows:

1. (Amended) An apparatus for performing parallel, independently controlled molecular reactions, comprising:

(a) a substantially monolithic structure formed from a plurality of green-sheet layers sintered together, said green-sheet layers including particles selected from the group consisting of ceramic particles, glass particles, and glass-ceramic particles; ~~supporting substrate comprising a ceramic layer,~~

(b) said ~~substrate~~ substantially monolithic structure comprising ~~channels and vias defining~~ a plurality of separate well structures separated by thermal insulating material,

(c) a heater associated with each well structure,

(d) a cooling element associated with each well structure, and

(e) a temperature monitor associated with each well structure.~~; and~~

~~(f) conductive pathways extending along and into the device, wherein the pathways make electrical connection to said heaters, coolers, or temperature monitors.~~

16. (Amended) The apparatus of Claim 15, wherein said metal wire resistive heater is integrated into said substantially monolithic structure ~~supporting substrate~~.

33. (Amended) The apparatus of Claim 1, wherein each of said heaters comprise ~~conductive~~ coils forming loops around each of said well structures along a length of said well structures.

Claims 34 and 35 were added.

Appendix A: Pending Claims

1. (Amended) An apparatus for performing parallel, independently controlled molecular reactions, comprising:

(a) a substantially monolithic structure formed from a plurality of green-sheet layers sintered together, said green-sheet layers including particles selected from the group consisting of ceramic particles, glass particles, and glass-ceramic particles;

(b) said substantially monolithic structure comprising a plurality of separate well structures separated by thermal insulating material,

(c) a heater associated with each well structure,

(d) a cooling element associated with each well structure, and

(e) a temperature monitor associated with each well structure.

2. The apparatus of Claim 1, wherein the molecular reaction is polymerase chain reaction.

6. The apparatus of Claim 1, wherein said heater is a resistive heater.

7. The apparatus of Claim 6, wherein the well structures are made of a thermal conducting material and are separated by said thermal insulating material.

8. The apparatus of Claim 7, wherein said thermal insulating material is glass, silicon, plastic, air contained in an air channel positioned proximal to the well structure, or ceramic.

10. The apparatus of Claim 7, wherein the thermal conducting material is undoped silicon, modified plastics, silver, silver palladium, copper, nickel-molybdenum, platinum, or gold and the thermal insulating material is glass, silicon, plastic, ceramic, or air contained in an air channel positioned proximal to the well structure.

11. The apparatus of Claim 1, wherein the well structures are coated with a compound that enhances biocompatibility between the components of the molecular reaction and said well structures.

12. The apparatus of Claim 11, wherein the compound coating is parylene.

14. The apparatus of Claim 1, wherein said heater is a thin film resistive heater.

15. The apparatus of Claim 1, wherein said heater is a metal wire resistive heater.

16. (Amended) The apparatus of Claim 15, wherein said metal wire resistive heater is integrated into said substantially monolithic structure.

17. The apparatus of Claim 14 or 15 or 33, wherein said heaters are controlled using column-and-row electrical addressing.

18. The apparatus of Claim 14 or 15 or 33, wherein said heaters are controlled using individual electrical addressing.

19. The apparatus of Claim 1, wherein said cooling element is a passive cooling system.

20. The apparatus of Claim 1, wherein said cooling element is an active cooling system.

21. The apparatus of Claim 20, wherein said active cooling system is an integrated cooling system.

22. The apparatus of Claim 21, wherein said integrated cooling system is selected from the group consisting of a metal plate, an array of metal discs, and a thermo-electric cooler, wherein said integrated cooling system is in thermal contact with each of the well structures.

23. The apparatus of Claim 1, wherein said temperature monitor is an integrated optical or electrochemical sensor system.

26. The apparatus of Claim 1, further comprising sealed well structures.

27. The apparatus of Claim 26, wherein the well structures are sealed using a layer of mineral oil.

28. The apparatus of Claim 26, wherein the well structures are sealed using a cover.

29. The apparatus of Claim 28, wherein the cover further comprises a heater.

30. The apparatus of Claim 28, wherein said heater is an integrated heating system.

31. The apparatus of Claim 1, wherein the thermal insulating material is plastic and said temperature monitor is an integrated resistive thermal detector molded into said plastic.

32. The apparatus of Claim 1, wherein the thermal insulating material is plastic and said temperatur monitor is a thermocouple molded into said plastic.

33. (Amended) The apparatus of Claim 1, wherein each of said heaters comprise coils forming loops around each of said well structures along a length of said well structures.

34. (New) The apparatus of Claim 1, further comprising electrical connections to said well structures distributed three-dimensionally within said substantially monolithic structure.

35. (New) The apparatus of Claim 1, further comprising conductive pathways extending along and into the device, wherein the pathways make electrical connection to said heaters, coolers, or temperature monitors.